

REMARKS**I. Amendment To The Specification**

The specification has also been amended to correct a number of spelling and grammatical errors, and correct its colloquial form. The errors that have been corrected appeared in the original Japanese application (JP 2003-93900) and were literally translated into English upon entry into the U.S. national phase. These amendments do not add new matter.

II. Claim Status

Upon entry of this amendment, Claims 1-8 are pending.

Claims 1, 5, 6, and 7 has been amended to limit the range for the number average molecular weight of PEG to 1000 to 7000. Support for this amendment is found in the specification on page 10, lines 9-13.

Claim 1 has also been amended to clarify that the PEG is bonded directly via cadmium to the II-VI semiconductor nanocrystals. Support for this amendment is found in the specification on page 5, lines 19-24 and page 12, lines 26-28.

All amendments are supported by the application as filed. By this amendment, no new matter has been added to the application.

III. Claim rejections. The claim rejections set forth in the Office Action are summarized and addressed as follows.

(I) Rejections under 35 U.S.C. § 103(a).

Claims 1-8 have been rejected as allegedly obvious over Bawendi et al. (U.S. Patent No. 6,251,303; "Bawendi I") and Bawendi et al. (U.S. Patent No. 6,444,143; "Bawendi II"). The Examiner asserts that, although neither Bawendi patent specifically teaches the number average

molecular weight (M_n) of polyethylene glycol (PEG) or such glycol bonded through cadmium, introduction of these variables would have been obvious to one having ordinary skill in the art. Specifically, the Examiner states that variation of the M_n of PEG would be routine to achieve an “optimum value of a result effective variable” (e.g., water solubility, increased quantum yield, etc), and that introduction of cadmium would have been obvious because it would “introduce covalent bonding between surface of nanoparticle and [PEG].”

In response, without conceding the validity of the rejection, Applicants have amended claims 1, 5, 6, and 7 to limit the M_n of PEG to “1000 to 7000.” Applicants have further amended claim 1 to recite that the polyethylene glycol having a thiol group at one end is “bonded directly via cadmium to II-IV semiconductor nanocrystals.” Although the Examiner alleges that varying the M_n of PEG and using cadmium to link the PEG to the nanocrystal are obvious, applicants respectfully submit that these features are not obvious because they have an unexpected advantage over the prior art.

Both Bawendi patents call for a *hydrophobic region* between the group linked directly to the nanoparticle (e.g., a thiol group) and the hydrophilic group used to impart aqueous solubility (e.g., PEG; *See* Bawendi II, col 3, lines 27-32 and col 7, lines 32-44). Bawendi also teaches that the hydrophobic region is *necessary* to “prevent photooxidation of the [nanoparticle] surface by charge transfer...” (*See* Bawendi II, col. 8, lines 53-63). Furthermore, the Bawendi patents teach that, in prior art examples where the hydrophobic region was absent, “luminescence is quenched and quantum yields are ‘unacceptably low’” (*See* Bawendi II, col 9, lines 1-9). The prior art aqueous soluble “quantum dots were not stable and photoluminescent properties degraded over time” (*See* Bawendi II, col. 2, lines 57-59, emphasis added). Thus, Bawendi suggests that the hydrophobic region taught in the Bawendi patents is necessary for the proper function of the technology because it insulates the nanoparticle from the “environment” (i.e., water) and prevents quenching of luminescence.

Applicants respectfully submit that it is surprising (and therefore not obvious) that the composition of the present innovation is luminescent even though there is no hydrophobic region,

but rather “direct” bonding of the PEG to the nanoparticle through cadmium. Support for “direct” bonding is found throughout the instant specification, for example on page 12, lines 26-28, where it is stated that “[t]he cadmium bonds to the thiol group of the PEG and to the shell surface of the semiconductor nanocrystals.” Additional support for the above arguments is found in Example 1 (See page 24, lines 7-12) where quenching of luminescence in an aqueous environment *does not* occur in the absence of the hydrophobic region deemed necessary by Bawendi. In Bawendi, the thiol-terminated PEG is not “directly” bonded to the ZnX outer shell.

To provide evidence for the significance of using PEG with an M_n of 1000 to 7000 and to demonstrate the unexpected effects of cadmium, The accompanying Rule 132 Declaration of inventor Atsuhiko Ogura (Exhibit 1) reports on comparative experiments with nanoparticles comprising PEG moieties of varying molecular weight. These experiments establish the significance of the molecular weight of PEG and the use of cadmium.

In Experiment 1 (Exh. 1, page 2), PEGs of various number average molecular weights were tested for effective binding to CdSe-ZnS nanoparticles in the presence of CdCl_2 , ZnCl_2 or no salt. A Zn salt was chosen for the study because Zn belongs to the same group of the Periodic Table (i.e., Group IIB) as Cd, and should therefore have chemical properties closely related to Cd. Effective binding between the nanoparticles and the thiol-terminated PEG was demonstrated by a change in solubility of the nanoparticles (i.e., nanoparticle partitioning in an organic/aqueous biphasic system). Accordingly, nanoparticles not effectively functionalized with PEG would remain soluble in chloroform whereas PEG-functionalized nanoparticles would partition into the aqueous phase.

As shown in Table 1, PEGs having an M_n of as low as 400, which is outside the scope of the present invention, were successfully bound to the nanoparticles irrespective of the salt. However, for PEGs having a molecular weight of 1000, efficient binding to the nanoparticles occurred only in the presence of CdCl_2 , whereas the presence of ZnCl_2 only slightly assisted binding. With PEGs of higher molecular weight, e.g., 2000, 5000, and 7000, the unique properties of CdCl_2 were even more apparent, as Zn no longer imparted aqueous solubility to the nanoparticles. It is thus demonstrated that, although PEGs with M_n as low as 400 are bound to the

semiconductor nanoparticles in the absence of cadmium, PEGs having the M_n of the presently claimed invention are not effectively bound without the assistance of cadmium.

Experiment 2 and Figure 1 (Exh 1, pages 2-4) provide data on the degree of aqueous stability of the nanoparticle Samples 1-7 from Table 1. Nanoparticle stability was determined by each samples ability to maintain fluorescence in aqueous solution over an extended period of time (e.g., 48 h). As shown in Figure 1, Samples 1-3 having a PEG M_n of 400, displayed a rapid decay in fluorescence over time. The samples of the presently claimed invention (Samples 4-7), however, exhibited substantially enhanced stability over the time course of the experiment. Thus, nanoparticles functionalized with PEG having an M_n of 1000 to 7000 wherein the PEG is directly bound to the nanoparticle via cadmium, provide the unexpected advantage of aqueous stability and thus maintain luminescence.

The surprising results reported in the Ogura declaration establish that the invention defined by the present claims is not obvious over the Bawendi I or Bawendi II references. The experiments described therein demonstrate that the use of cadmium for direct binding of PEG having an M_n of 1000 to 7000 provides for unexpected advantages in nanoparticle synthesis. Furthermore, the resultant nanoparticles are surprisingly stable in aqueous solution and display unexpected photoluminescent properties that are not degraded over time.

In summary, the inclusion of cadmium to bind thiol-terminated PEGs with an M_n from 1000 to 7000 to the semiconductor nanoparticles, as recited in currently amended claim 1, unexpectedly improves aqueous solubility and stability compared to the prior art. Using the invention defined by the present claims, stability and photoluminescent properties are maintained without the need for a *hydrophobic region* deemed necessary by Bawendi. Therefore, it is respectfully submitted that amended claim 1 is not obvious over Bawendi I and II. Because claim 1 is not obvious over Bawendi I and II, neither are claims 2-7 obvious over Bawendi I and II, as claims 2-7 either depend from or incorporate all of the limitations of claim 1. Reconsideration of claims 1-8 and withdrawal of the rejection under section 103 is respectfully requested.

CONCLUSION

Based on the preceding amendments and arguments, this application is believed to be in condition for allowance which is earnestly solicited.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: August 19, 2005

Respectfully submitted,

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